

# Degenerative aortic stenosis

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Aortic stenosis is the most common valvular lesion in Europe and North America. It primarily presents as calcific aortic stenosis in 2-7% of the population aged >65 years.<sup>1</sup> About 80% of adult patients with symptomatic aortic stenosis are male. As 1-2% of the population is born with a congenital bicuspid aortic valve and populations are ageing, aortic stenosis is becoming more common. By 2020, about 3.5 million people in England are expected to have aortic sclerosis and 150 000 will have severe aortic stenosis.<sup>2</sup> Here we provide an overview to help diagnosis and a summary of the management of AS and its sequelae. Many of the points made in this review are based on randomised controlled trials. However, observational studies and the guideline recommendations of the American Heart Association and the American College of Cardiology and of the European Society of Cardiology are also included to provide comprehensive overviews that are beyond the scope of this article.

## What are the factors leading to aortic stenosis?

The most common cause of aortic stenosis in adults is calcification of a normal trileaflet (fig 1). Calcific aortic stenosis is thought to be a degenerative process that shares many features with coronary artery disease, such as lipid accumulation, inflammation, and calcification. The abnormal architecture of the bicuspid or

unicuspid aortic valve makes the leaflets susceptible to haemodynamic stress, leading to valvular thickening, calcification, and increased rigidity and narrowing of the aortic orifice.

Aortic stenosis may also be secondary to rheumatic inflammation of the valve leaflets. Investigators have found histological similarities between the lesion of aortic stenosis and atheromatous coronary artery disease and have documented an association between traditional atherosclerotic risk factors and the development of calcific aortic valve disease.<sup>3</sup> Mature lamellar bone formation and osteopontin bone expression are present in calcified aortic valves. Researchers have also shown that hypercholesterolaemia can induce both cellular proliferation and osteoblast phenotype expression that may lead to progression of aortic valvular disease.<sup>4</sup>

## How is the haemodynamic severity of aortic stenosis classified?

In 2006 the American Heart Association and the American College of Cardiology jointly provided the guidelines in grading aortic stenosis (box 1) as mild, moderate, and severe (figs 2 and 3) (see [www.americanheart.org](http://www.americanheart.org)).<sup>5</sup>

Recently, the European Society of Cardiology (ESC) has also published guidelines (a summary is at [www.esc](http://www.esc)).

### Box 1 Grading of aortic stenosis<sup>5</sup>

#### Mild stenosis

Area >1.5 cm<sup>2</sup>

Mean gradient <25 mm Hg

Aortic jet velocity <3 m/s

#### Moderate stenosis

Area 1.0-1.5 cm<sup>2</sup>

Mean gradient 25-40 mm Hg

Aortic jet velocity 3-4 m/s

#### Severe stenosis

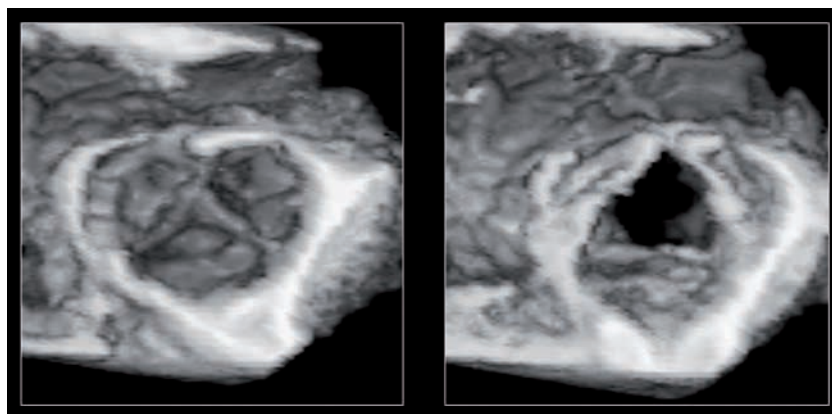
Area <1.0 cm<sup>2</sup>

Mean gradient >40 mm Hg

Aortic jet velocity >4 m/s

### SOURCES AND SELECTION CRITERIA<sup>1</sup>

The literature search included Medline and PubMed from 2003 to the present. The terms searched were "aortic stenosis", "diagnosis", "aortic valve replacement", and "grading" in various combinations. We scrutinised the articles identified by this search and selected high quality randomised controlled trials and retrospective studies. We examined citation lists from these for further relevant articles. To identify the factors contributing to aortic stenosis, we did a complete search of the Medline database. When appropriate, we also considered publications from before 2003. We included some review articles, websites, and book chapters because they provide comprehensive overviews that are beyond the scope of this article.



**Fig 1** | Three dimensional transoesophageal echocardiographic image at the level of the tricuspid aortic valve, displayed from the perspective of the aortic root (looking into the left ventricular cavity) in a patient with a widely patent trileaflet aortic valve (left panel shows diastole, right panel shows systole)

escardio.org).<sup>6</sup> Aortic stenosis produces a systolic gradient between the left ventricular outflow tract and the aorta. Aortic sclerosis is distinguished from aortic stenosis by the valve thickening and calcification without obstruction (no significant gradient) (fig 1). However, 16% of patients with aortic sclerosis will progress to aortic stenosis in seven years time.<sup>7</sup>

#### How do we diagnose aortic stenosis?

##### Clinical diagnosis

The patient's history and physical examination are essential in diagnosing aortic stenosis. Identifying symptoms such as exertional shortness of breath,

angina, dizziness, or syncope is important for proper management. The characteristic systolic murmur guides further diagnostic investigations. An early peaking murmur is usually associated with a less stenotic valve, whereas a late peaking murmur has a more severe degree of stenosis. This is because a more stenotic valve takes longer for the ventricle to generate the pressures needed to force the blood past the lesion. Occasionally, the murmur may be faint and primary presentation may be heart failure of unknown cause. The disappearance of the second aortic sound is specific to severe aortic stenosis, although not a sensitive sign.<sup>7</sup> The murmur of aortic stenosis is often "missed" (or not understood for what it is) in many patients, especially in those who are obese or have underlying obstructive lung diseases (where the murmur is muffled) and in those with left ventricular dysfunction (where the murmur is blunted).

##### Radiological diagnosis

Echocardiography has become the key diagnostic tool to confirm the presence of aortic stenosis; assess the degree of valve calcification, left ventricular function, and wall thickness; detect the presence of other associated valve disease; and provide prognostic information. Doppler echocardiography is the preferred technique for assessing severity. Aortic stenosis with a valve area  $<1.0 \text{ cm}^2$  is considered severe; however, when patients have unusually small or large body surface area, a cut-off value of  $0.6 \text{ cm}^2/\text{m}^2$  is helpful.<sup>8</sup>

##### What is the natural course of aortic stenosis?

The process of maintaining cardiac output against the aortic stenosis gradient leads to left ventricular hypertrophy. Increased muscle mass of the left ventricle raises myocardial oxygen consumption. In severe aortic stenosis, even in the absence of narrowing of the coronary arteries, the increased stress on the left ventricular wall and workload demands, coupled with direct ventricular pressure compressing the coronary arteries during diastolic flow, may exceed adequate coronary perfusion pressure and cause myocardial ischaemia and angina. Left ventricular diastolic dysfunction is widespread, and left ventricular systolic dysfunction is not uncommon; both these conditions produce symptoms of congestive cardiac failure.

After the onset of symptoms, the average survival is only two to three years. On the basis of the data obtained at postmortem examination in patients not treated surgically, the average time to death after the onset of various symptoms was as follows: angina, three years; syncope, three years; dyspnoea, two years; and congestive cardiac failure, one and a half to two years. Conversely, asymptomatic patients even with severe aortic stenosis have an excellent prognosis without aortic valve replacement. However, the duration of the asymptomatic phase varies widely among individuals. Unfortunately, at least 1-2% of asymptomatic patients die suddenly or have very rapid rate of

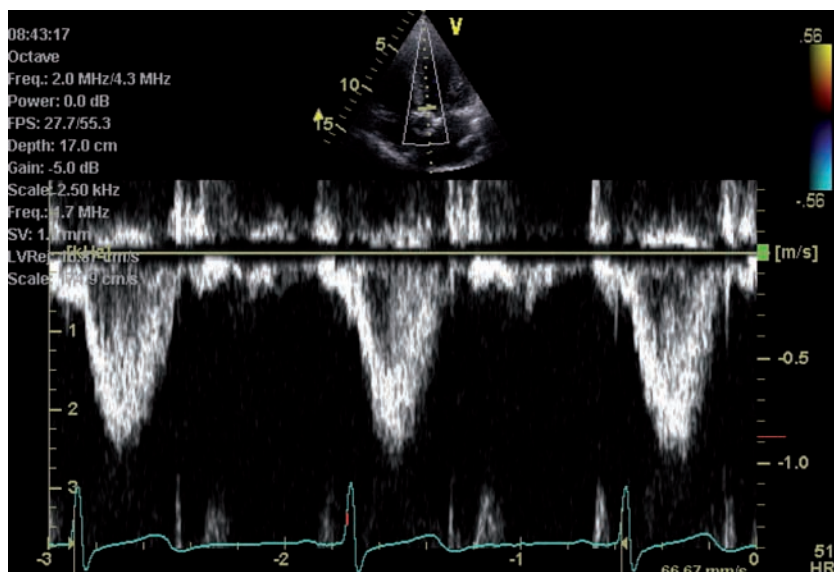
#### Box 2 Joint Recommendations of American Heart Association and American College of Cardiology for aortic valve replacement in patients with aortic stenosis<sup>5</sup>

##### Aortic valve replacement indicated

- In patients with severe aortic stenosis with its classic "SAD" symptoms (syncope, angina, and/or dyspnoea)
- In patients with severe aortic stenosis who are having coronary artery bypass grafting
- In patients with severe aortic stenosis having surgery on the aorta or other heart valves
- In patients with severe aortic stenosis with left ventricular systolic dysfunction (ejection fraction  $<50\%$ )

##### Aortic valve replacement possibly indicated

- In patients with moderate aortic stenosis having coronary artery bypass grafting or surgery on the aorta or other heart valves
- In patients with asymptomatic severe aortic stenosis with abnormal response to exercise (such as development of symptoms or asymptomatic hypotension)
- In patients with asymptomatic severe aortic stenosis if there is likelihood of rapid progression (age, calcification, and coronary artery disease) or if surgery might be delayed at the time of symptom onset
- In patients with mild aortic stenosis having coronary artery bypass grafting when there is evidence of moderate to severe calcification, suggesting that progression is likely and may be rapid
- In patients with asymptomatic extreme severe aortic stenosis (aortic valve area  $<0.6 \text{ cm}^2$ , mean gradient  $>60 \text{ mm Hg}$ , or a jet velocity  $>5 \text{ m/s}$ ) when the patient's expected operative mortality is  $\leq 1\%$



**Fig 2 | Pulsed wave Doppler echocardiogram in patient with severe aortic stenosis: transthoracic, two dimensional, apical, five chamber view (inset). A pulsed wave Doppler region of interest (sample volume) is placed proximal to the stenotic aortic valve in the left ventricular outflow tract, and the spectral display is shown. At 1.0 m/s, the blood flow velocity in the left ventricular outflow tract is equivalent to a gradient of 4 mm Hg**

progression to symptomatic stage and then to sudden death.<sup>9</sup> Among patients with congenital or degenerative disease, progression to valve replacement occurs earliest if the patient has a unicuspid valve, later in the case of a bicuspid valve, and latest with a tricuspid valve.

#### What are the medical treatments for aortic stenosis?

When symptoms develop, mortality rises sharply, so standard therapeutic guidelines recommend surgery.<sup>5,6</sup> No effective drug treatment exists for severe aortic stenosis, and only a few drugs are available to alleviate symptoms. Patients with evidence of pulmonary congestion can benefit from cautious treatment with digitalis or diuretics, or both. A recent observational, drug withdrawal, single blinded study, with randomisation of the order of tests supports the concept that angiotensin converting enzyme inhibitors are safe and

#### Box 3 Recommendations of European Society of Cardiology for follow-up in patients with aortic stenosis<sup>6</sup>

- Follow-up visits should include echocardiographic assessment
- Patients with moderate to severe calcification of the valve and peak aortic jet velocity  $>4$  m/s should be re-evaluated every six months
- If peak aortic jet velocity increases by  $>0.3$  m/s per year or if other evidence of haemodynamic progression is present, surgery should be considered
- If the patient remains asymptomatic, clinical re-evaluations every six months and echocardiographic re-evaluations every six to 12 months are recommended

#### TIPS FOR NON-SPECIALISTS

- Careful physical examination of elderly patients can help to identify aortic stenosis
- Use SAD criteria (syncope, angina, and dyspnoea) to evaluate symptoms
- Aortic valve replacement is indicated for symptomatic aortic stenosis, regardless of age, and can save lives
- Aortic valve replacement is not indicated in the absence of symptoms
- An early peaking murmur is usually associated with a less stenotic valve, whereas a late peaking murmur has a more severe degree of stenosis
- The murmur of critical aortic stenosis is soft when the patient has left ventricular dysfunction
- Perform echocardiography whenever aortic stenosis is considered, and repeat according to onset or progression of symptoms
- Coronary angiography is usually needed before aortic valve replacement, except in young patients
- Endocarditis prophylaxis is indicated in all patients with aortic stenosis

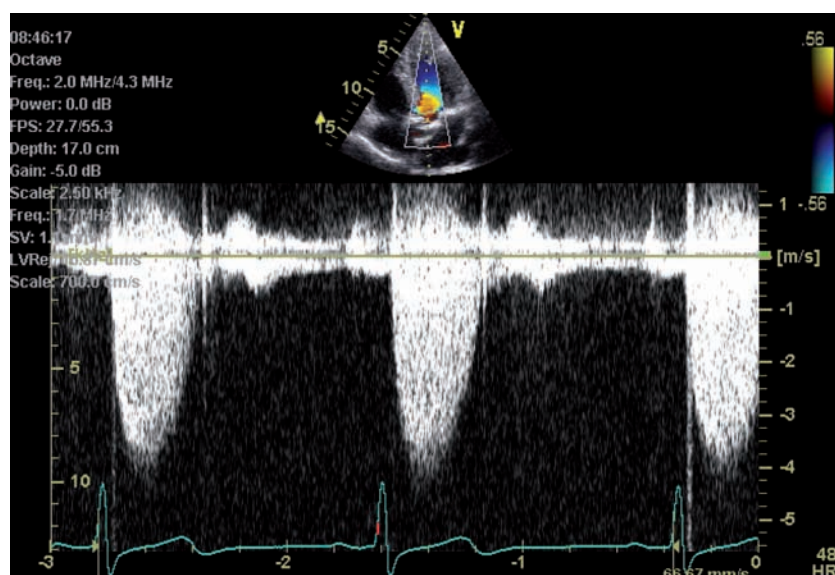
may provide short term benefit to patients with aortic stenosis.<sup>10</sup> In patients with aortic stenosis, the afterload reduction caused by angiotensin converting enzyme inhibitors is partially blunted by a parallel increase in the transvalvular pressure gradient. However, angiotensin converting enzyme inhibitors favourably affect stress haemodynamic variables in most hypertensive patients with aortic stenosis. A prospective, single blinded study conducted at Cleveland clinic, Ohio, showed that in patients with acute pulmonary oedema, left ventricular systolic dysfunction, and aortic stenosis nitroprusside infusion may help to reduce congestion and improve symptoms.<sup>11</sup> Atrial fibrillation has an adverse effect on atrial pump function and ventricular rate, hence prompt cardioversion is beneficial. Endocarditis prophylaxis is indicated in all patients with aortic stenosis.<sup>12</sup>

No medical treatment has been proved to prevent or delay the disease process in the aortic valve leaflets. The association of aortic stenosis with clinical features similar to atherosclerosis has led to the hypothesis that aggressive modification of risk factors, as for coronary heart disease, may slow or prevent disease progression in the valve leaflets. Despite this hope, recent reports using statins have shown mixed results: one study failed to show a beneficial effect,<sup>13</sup> whereas another study showed that rosuvastatin can slow the haemodynamic progression of aortic stenosis.<sup>14</sup>

#### What is the definitive treatment for aortic stenosis?

Aortic stenosis is a mechanical obstruction, hence requires mechanical correction. Studies have shown that once symptoms develop, a patient's life span is severely shortened unless the valve is replaced (fig 4). In contrast, age corrected 10 year survival rates among patients who had surgery for aortic valve replacement





**Fig 3** | Continuous wave Doppler echocardiogram in patient with severe aortic stenosis (same patient as in figure 2). Transthoracic, two dimensional, apical, five chamber view (inset). A continuous wave Doppler records the maximal velocity across the narrowest point of the stenotic aortic valve and the spectral display is shown. The ratio of the velocity of the blood flow in the left ventricular outflow tract (1 m/s) to the aortic jet velocity (4.5 m/s) is  $<0.25$ , which is consistent with severe aortic stenosis

approach the survival rate in the normal population.<sup>16</sup> Therefore, in the absence of any serious comorbid conditions, aortic valve replacement is indicated in virtually all symptomatic patients with severe aortic stenosis, even in very elderly people.<sup>5</sup> Balloon valvuloplasty is not recommended in adults but can be used as a bridge to surgery in haemodynamically unstable patients who are at high risk of surgery or in patients with symptomatic severe aortic stenosis who require urgent, major non-cardiac surgery.<sup>6</sup>

Most patients aged  $>40$ -45 years require coronary angiography before aortic valve replacement to exclude coexistent coronary artery disease. Grading or reconfirmation of aortic stenosis is also possible

during this procedure if the diagnosis remains uncertain after echocardiography. About 40% of patients having aortic valve replacement have severe coronary artery disease and require concurrent coronary bypass grafting. Preliminary reports show that percutaneous aortic valve replacement is feasible, but this procedure is not often done yet and further studies are needed to evaluate its potential role.<sup>17</sup> Asymptomatic patients with severe aortic stenosis generally have an excellent prognosis without aortic valve replacement. In patients with left ventricular dysfunction and severe aortic stenosis, the outcome after replacement surgery is excellent despite the presence of a reduced ejection fraction preoperatively.<sup>18</sup> Excessive afterload may contribute to the left ventricular dysfunction, which often returns to normal once obstruction is relieved.

### Is age a contraindication for aortic valve replacement?

A prospective Swedish study and an observational study show that aortic valve replacement improves symptoms and survival in patients with severe aortic stenosis.<sup>16,18</sup> Age is not a contraindication to surgery, with studies showing similar outcomes to those in age matched normal subjects in very elderly people. The operative risks can be estimated with readily available and a well validated online risk calculator from the European System for Cardiac Operative Risk Evaluation ([www.euroscore.org](http://www.euroscore.org)).<sup>19</sup> Indications for aortic valve replacement (fig 5) are given in the guidelines of the American Heart Association and the American College of Cardiology (box 2)<sup>5</sup> and of the European Society of Cardiology.<sup>6</sup> Doppler echocardiography should be done for the initial evaluation of patients suspected of having aortic stenosis, as well as in patients with established disease if symptoms develop or physical signs change. Box 3 outlines the European Society of Cardiology's recommendations for follow-up in patients with aortic stenosis.

#### Box 4 Predictors of progression of aortic stenosis<sup>6</sup>

##### Clinical

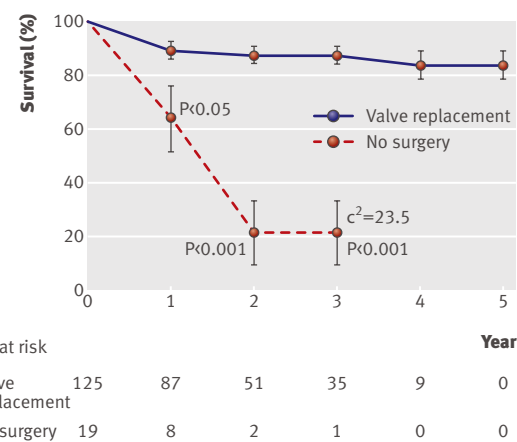
Older age  
Atherosclerotic risk factors

##### Echocardiography

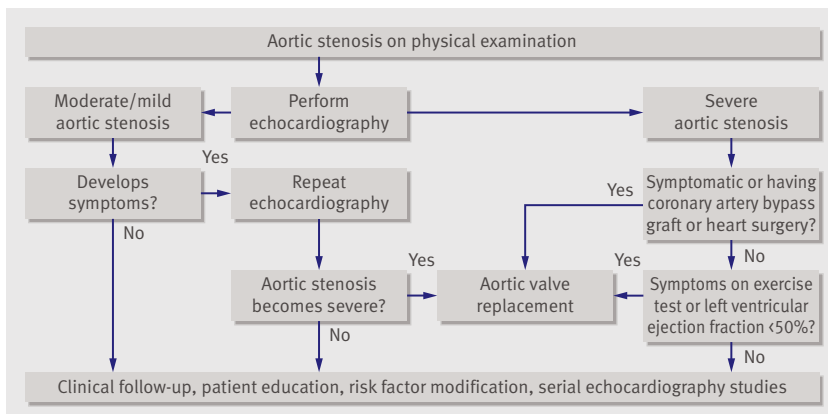
Valve calcification  
Peak aortic jet velocity (increase of 0.3 m/s per year)  
Decrease in left ventricular ejection fraction  
Haemodynamic progression  
Increase in gradient with exercise

##### Exercise testing

Development of symptoms on exercise testing  
Abnormal blood pressure response  
ST segment depression



**Fig 4** | Kaplan-Meier survival curve for patients with severe symptomatic aortic stenosis who had valve replacement and similar patients who declined surgery. Adapted from Schwarz F et al<sup>15</sup>



**Fig 5 | Proposed algorithm of treatment of aortic stenosis based on 2006 guidelines of American Heart Association and American College of Cardiology for management of patients with valvular heart disease**

#### ONGOING RESEARCH

Some of the many trials currently testing the effects of statins in aortic valve disease are listed below.

*STOP-AS*—Stop aortic stenosis (Cleveland Clinic, Cleveland, Ohio, USA)

*SEAS*—Simvastatin and the ezetimibe in aortic stenosis (Europe)

*ASTRONOMER*—Aortic stenosis progression observation measuring effects of rosuvastatin (Canada)

#### How can the progression of aortic stenosis be predicted?

The rate of progression of aortic stenosis in an individual patient cannot be predicted but is reportedly more rapid in patients with degenerative calcific disease than in those with congenital or rheumatic disease. Some studies suggest that the rate of haemodynamic progression is faster when the patient is aged over 50 years and has severe calcification or concurrent coronary heart disease.<sup>20</sup> Preliminary studies have shown that natriuretic peptides predict symptom-free survival in aortic stenosis.<sup>21</sup> Box 4 summarises the predictors of the progression of aortic stenosis and therefore of poor outcome in asymptomatic patients.<sup>6</sup>

#### ADDITIONAL EDUCATIONAL RESOURCES

- Joint guidelines from the American Heart Association and the American College of Cardiology and guidelines from the European Society of Cardiology for the treatment of valvular heart diseases are available at [www.americanheart.org](http://www.americanheart.org) and [www.escardio.org](http://www.escardio.org) respectively
- Article on aortic stenosis from cardiology department in Cleveland clinic, Ohio, at [www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/aortic\\_valve/aortic\\_valve.htm](http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/aortic_valve/aortic_valve.htm)

#### UNANSWERED RESEARCH QUESTIONS

- Does calcific aortic valve stenosis have an active process of progression, similar to atherosclerosis, that medical treatment may be proved to modify?
- Can lifestyle modifications or the use of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) retard the progression of aortic stenosis?
- Do patients with asymptomatic mild or moderate aortic stenosis who are having cardiac surgery need valve replacement?
- Given the low operative mortality, will elective aortic valve replacement ever be recommended for asymptomatic severe aortic stenosis to reduce subsequent morbidity and mortality?

The presence of low cardiac output may lead clinicians to an incorrect assessment of the severity of the aortic stenosis. Patients with low cardiac output usually have small aortic valve areas (suggesting severe aortic stenosis) but also low aortic valve gradients (suggesting a mild or moderate condition). This discrepancy can be distinguished by recalculating the valve area after increasing cardiac contractility with inotropic stimulation (usually dobutamine). Truly severe aortic stenosis shows only small changes in valve area (increase  $<0.2 \text{ cm}^2$ ) with increasing flow rate but a substantial increase in gradients (mean gradient  $>50 \text{ mm Hg}$ ). “Pseudosevere” aortic stenosis, however, shows a marked increase in valve area but only minor changes in gradients.<sup>22</sup> Patients with true severe aortic

#### Differences between the European and the US guidelines\*

- Mild, moderate, and severe aortic stenosis are defined in the US guidelines, but only severe and moderate aortic stenosis are defined in the European guidelines
- The US guidelines recommend follow-up of patients with aortic stenosis as below, but the European guidelines are different (see box 3):
  - In patients with severe aortic stenosis, echocardiography every year may be appropriate
  - In patients with moderate aortic stenosis, serial studies every one to two years are satisfactory
  - In patients with mild AS, serial studies can be performed every 3 to 5 years.
- The US guidelines do not recommend using balloon valvuloplasty in adults because of high rate of complications ( $>10\%$ ) and restenosis. But the European guidelines recommend balloon valvuloplasty in certain circumstances, such as in haemodynamically unstable patients who are at high risk surgically or in patients with symptomatic severe aortic stenosis who require urgent, major non-cardiac surgery

\*The guidelines of the European Society of Cardiology, and the joint guidelines of the American Heart Association and American College of Cardiology.

## SUMMARY POINTS

Although aortic stenosis is common, its diagnosis may be missed

Calcific aortic stenosis shares many common features with atherosclerosis

After the onset of symptoms, the average survival is two to three years, and patients with symptoms of syncope, angina, and dyspnoea need prompt aortic valve replacement

Endocarditis prophylaxis is indicated in all patients with aortic stenosis

Echocardiography should be performed once aortic stenosis is suspected.

Coronary artery angiography is usually needed before aortic valve replacement, except in young patients

Careful exercise testing should be considered in asymptomatic patients with severe aortic stenosis who are sedentary or unable to give a clear history

stenosis benefit from aortic valve replacement, but those with pseudosevere aortic stenosis would not benefit and could be harmed. Decreased contractile response ( $<20\%$  of stroke volume) to inotropic infusion indicates a very poor clinical outcome and high mortality.

## Conclusion

Clinicians should aim to diagnose aortic stenosis early in the physical examination, to document the severity with echocardiography while the patient is apparently asymptomatic, and try to predict whether the patient has the highest likelihood of developing symptoms. Elective surgery should be planned at the earliest onset of symptoms and requires careful clinical observation. When the history is unclear or the patient is sedentary, carefully supervised exercise tests should be done to identify the early onset of cardinal symptoms. As explained earlier, age is not a contraindication to aortic valve replacement.

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